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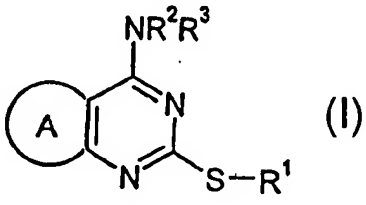
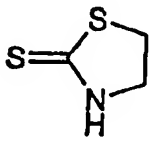
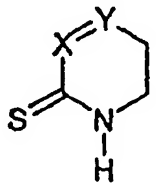
(54) Title: THIAZOLOPYRIMIDINES AND THEIR USE AS MODULATORS OF CHEMOKINE RECEPTOR ACTIVITY



(I)



(a)



(b)

(57) Abstract: The invention provides certain thiazolopyrimidine compounds of formula (I) or a pharmaceutically acceptable salt or solvate thereof: in which: A is a group of formula (a) or (b): processes and intermediates used in their preparation, pharmaceutical compositions containing them and their use in therapy.

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THIAZOLOPYRIMIDINES AND THEIR USE AS MODULATORS OF CHEMOKINE RECEPTOR ACTIVITY

The present invention relates to certain heterocyclic compounds, processes and intermediates used in their preparation, pharmaceutical compositions containing them and their use in therapy.

Chemokines play an important role in immune and inflammatory responses in various diseases and disorders, including asthma and allergic diseases, as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis. These small secreted molecules are a growing superfamily of 8-14 kDa proteins characterised by a conserved four cysteine motif. At the present time, the chemokine superfamily comprises three groups exhibiting characteristic structural motifs, the Cys-X-Cys (C-X-C), Cys-Cys (C-C)) and Cys-X_3-Cys (C-X_3-C) families. The C-X-C and C-C families have sequence similarity and are distinguished from one another on the basis of a single amino acid insertion between the NH-proximal pair of cysteine residues. The C-X_3-C family is distinguished from the other two families on the basis of having a triple amino acid insertion between the NH-proximal pair of cysteine residues.

The C-X-C chemokines include several potent chemoattractants and activators of neutrophils such as interleukin-8 (IL-8) and neutrophil-activating peptide 2 (NAP-2).

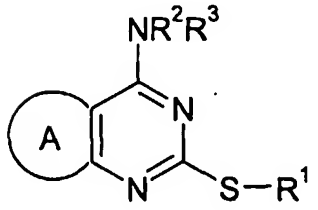
The C-C chemokines include potent chemoattractants of monocytes and lymphocytes but not neutrophils. Examples include human monocyte chemotactic proteins 1-3 (MCP-1, MCP-2 and MCP-3), RANTES (Regulated on Activation, Normal T Expressed and Secreted), eotaxin and the macrophage inflammatory proteins 1α and 1β (MIP-1α and MIP-1β).

The C-X_3-C chemokine (also known as fractalkine) is a potent chemoattractant and activator of microglia in the central nervous system (CNS) as well as of monocytes, T cells, NK cells and mast cells.

Studies have demonstrated that the actions of the chemokines are mediated by subfamilies of G protein-coupled receptors, among which are the receptors designated CCR1, CCR2, CCR2A, CCR2B, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10 and CCR11 (for the C-C family); CXCR1, CXCR2, CXCR3, CXCR4 and CXCR5 (for the C-X-C family) and CX_3CR1 for the C-X_3-C family. These receptors represent good targets for

drug development since agents which modulate these receptors would be useful in the treatment of disorders and diseases such as those mentioned above.

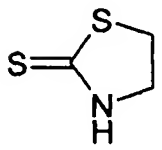
The present invention therefore provides compounds of formula (I) and pharmaceutically acceptable salts or solvates thereof:



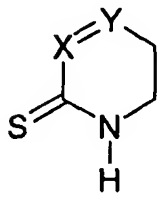
(I)

in which:

A is a group of formula (a) or (b):



(a)



(b)

R^1 represents a C_3-C_7 carbocyclic, C_1-C_8 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl group, each of which may be optionally substituted by one or more substituent groups independently selected from halogen atoms, $-OR^4$, $-NR^5R^6$, $-CONR^5R^6$, $-COOR^7$, $-NR^8COR^9$, $-SR^{10}$, $-SO_2R^{10}$, $-SO_2NR^5R^6$, $-NR^8SO_2R^9$, an aryl or heteroaryl group, which last two may themselves be optionally substituted by one or more substituents independently selected from halogen atoms, cyano, nitro, $-OR^4$, $-NR^5R^6$, $-CONR^5R^6$, $-COOR^7$, $-NR^8COR^9$, $-SR^{10}$, $-SO_2R^{10}$, $-SO_2NR^5R^6$, $-NR^8SO_2R^9$, C_1-C_6 alkyl or trifluoromethyl groups;

R^2 and R^3 each independently represent a hydrogen atom, or a C_3-C_7 carbocyclic, C_1-C_8 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl group, the latter four groups may be optionally substituted by one or more substituent groups independently selected from:

(a) halogen atoms, $-OR^4$, $-NR^5R^6$ $-CONR^5R^6$, $-COOR^7$, $-NR^8COR^9$, $-SR^{10}$, $-SO_2R^{10}$, $-SO_2NR^5R^6$, $-NR^8SO_2R^9$;

(b) a 3-8 membered ring optionally containing one or more atoms selected from O, S, NR^8 and itself optionally substituted by C_1-C_3-alkyl or halogen; or

(c) an aryl group or heteroaryl group each of which may be optionally substituted by one or more substituents independently selected from halogen atoms, cyano, nitro, $-OR^4$, $-NR^5R^6$, $-CONR^5R^6$, $-NR^8COR^9$, $-SO_2NR^5R^6$, $-NR^8SO_2R^9$, C_1-C_6 alkyl and trifluoromethyl groups;

R^4 represents hydrogen, C_1-C_6 alkyl or a phenyl group the latter two of which may be optionally substituted by one or more substituent groups independently selected from halogen atoms, phenyl, $-OR^{11}$ and $-NR^{12}R^{13}$

R^5 and R^6 independently represent a hydrogen atom or a C_1-C_6 alkyl or phenyl group the latter two of which may be optionally substituted by one or more substituent groups independently selected from halogen atoms, phenyl, $-OR^{14}$ and $-NR^{15}R^{16}$, $-CONR^{15}R^{16}$, $-NR^{15}COR^{16}$, $-SONR^{15}R^{16}$, $NR^{15}SO_2R^{16}$

or

R^5 and R^6 together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocyclic ring system optionally containing a further heteroatom selected from oxygen and nitrogen atoms, which ring system may be optionally substituted by one or more substituent groups independently selected from phenyl, $-OR^{14}$, $-COOR^{14}$, $-NR^{15}R^{16}$, $-CONR^{15}R^{16}$, $-NR^{15}COR^{16}$, $-SONR^{15}R^{16}$, $NR^{15}SO_2R^{16}$ or C_1-C_6 alkyl, itself optionally substituted by one or more substituents independently selected from halogen atoms and $-NR^{15}R^{16}$ and $-OR^{17}$ groups;

R^{10} represents a C_1-C_6-alkyl or a phenyl group, either of which may be optionally substituted by one or more substituent groups independently selected from halogen atoms, phenyl, $-OR^{17}$ and $-NR^{15}R^{16}$,

X is CH or CCN,

Y is N or CR^{18}, and

each of R^7, R^8, R^9, R^{11}, R^{12}, R^{13}, R^{14} R^{15}, R^{16}, R^{17} and R^{18} independently represents a hydrogen atom or a C_1-C_6, alkyl, or a phenyl group.

In the context of the present specification, unless otherwise indicated, an alkyl or alkenyl group or an alkyl or alkenyl moiety in a substituent group may be linear or branched.

Aryl groups include phenyl and naphthyl. Heteroaryl is defined as a 5- or 6-membered aromatic ring optionally containing one or more heteroatoms selected from N, S, O. Examples include pyridine, pyrimidine, thiazole, oxazole, pyrazole, imidazole, furan.

Certain compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of the compounds of formula (I) and mixtures thereof including racemates. Tautomers and mixtures thereof also form an aspect of the present invention.

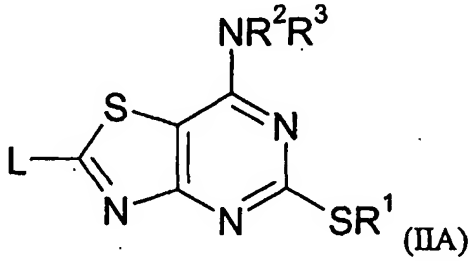
Suitably the group R^1 represents a C_3-C_7 carbocyclic, C_1-C_8 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl group, each of which may be may be optionally substituted by one or more substituent groups independently selected from halogen atoms, $-OR^4$, $-NR^5R^6$, $-CONR^5R^6$, $-COOR^7$, $-NR^8COR^9$, $-SR^{10}$, $-SO_2R^{10}$, $-SO_2NR^5R^6$, $-NR^8SO_2R^9$, an aryl or heteroaryl group both of which can be optionally substituted by one or more substituents independently selected from halogen atoms, cyano, nitro, $-OR^4$, $-NR^5R^6$, $-CONR^5R^6$, $-COOR^7$, $-NR^8COR^{10}$, $-SR^{10}$, $-SO_2R^{10}$, $-SO_2NR^5R^6$, $-NR^8SO_2R^{10}$, C_1-C_6 alkyl or trifluoromethyl groups. Particularly advantageous compounds of formula (I) are those in which R^1 represents an optionally substituted benzyl group. More preferably R^1 represents benzyl or benzyl substituted by one or more C_1-C_6 alkyl, C_1-C_6 alkoxy, or halogen atoms, in particular benzyl substituted by two fluoro atoms.

Preferably one of R^2 and R^3 is hydrogen and the other is C_1-C_8 alkyl substituted by hydroxy and one or more methyl or ethyl groups. More preferably one of R^2 and R^3 is hydrogen and the other is $CH(CH_3)CH_2OH$, $CH(Et)CH_2OH$, $C(CH_3)_2CH_2OH$ or $CH(CH_2OH)_2$. When one of R^2 and R^3 is hydrogen and the other is $CH(CH_3)CH_2OH$ or $CH(Et)CH_2OH$ the resulting compounds of formula (I) are preferably in the form of the (R) isomer. Most preferably one of R^2 and R^3 is hydrogen and the other is $CH(CH_3)CH_2OH$.

Suitably in formula (b) X represents CH or CCN and Y is N or CR^{18}. Preferably X is CH and Y is N.

Particularly preferred compounds of the invention include:
5-[[(2,3-difluorophenyl)methyl]thio]-7-[[(1*R*)-2-hydroxy-1-methylethyl]amino]-thiazolo[4,5-*d*]pyrimidine-2(3*H*)-thione,
2-[[(2,3-difluorophenyl)methyl]thio]-4-[[(1*R*)-2-hydroxy-1-methylethyl]amino]-7(8*H*)-pteridinethione,
and pharmaceutically acceptable salts thereof.

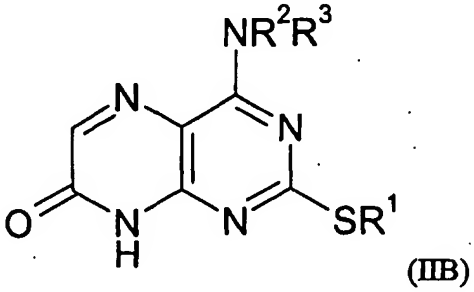
According to the invention there is also provided a process for the preparation of a compound of formula (I) which comprises:
(a) treatment of a compound of formula (IIA):



(IIA)

where R^1, R^2 and R^3 are as defined in formula (I) or are protected derivatives thereof and L is a leaving group with a metal hydrosulphide, or

(b) treatment of a compound of formula (IIB):



(IIB)

where R^1, R^2 and R^3 are as defined in formula (I) or are protected derivatives thereof with a thiating agent, and optionally thereafter process (a) or (b) and in any order:

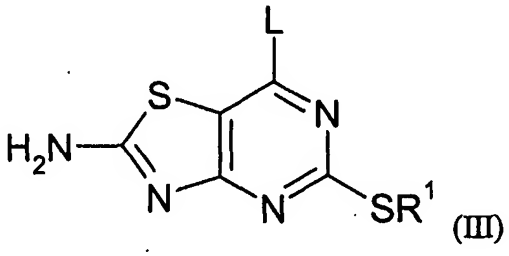
- removing any protecting groups
- forming a pharmaceutically acceptable salt.

The reaction of compounds of formula (IIA) with a metal hydrosulphide may be carried out in a solvent such as DMSO at a temperature between 0°C and 100°C. Suitable leaving groups L include halogen, especially chloro or bromo, and a suitable metal hydrosulphide is sodium hydrosuphide.

The reaction of compounds (IIB) with a thiating agent may be carried out in a solvent such as dioxan at reflux. A suitable thiating agent is Lawesson's reagent.

Compounds of formula (IIA) where R^1, R^2 and R^3 are as defined in formula (I) and L is a leaving group may be prepared from compounds of formula (IIA) where R^1, R^2 and R^3 are as defined above and L is NH_2 by treatment with sodium nitrite and aqueous mineral acid at a temperature between 0°C and room temperature. Suitable acids include hydrochloric acid.

Compounds of formula (IIA) where R^1, R^2 and R^3 are as defined in formula (I) and L is NH_2 may be prepared by treatment of a compound of formula (III):



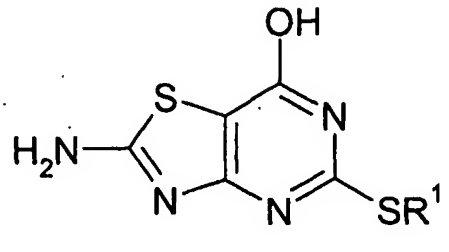
(III)

where R^1 is as defined in formula (I) and L is a leaving group such as chlorine with an amine HNR^2R^3 where R^2 and R^3 are as defined in formula (I). The reaction may be carried out in a solvent such as *N*-methyl-pyrrolidine at a temperature between 0°C and 150°C.

Compounds of formula (III) where R^1 is as defined in formula (I) and L is a halogen may be prepared by treating a compound of formula (III) where R^1 is as defined in formula (I) and L is a hydroxyl group with a halogenating agent such as phosphorous oxychloride. The reaction may be carried out in the presence of dimethylaniline at reflux.

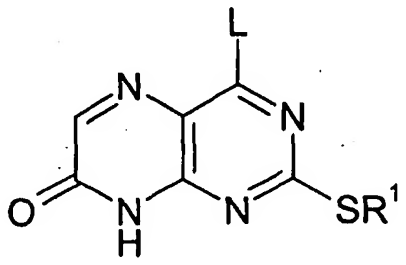
Compounds of formula (III) where R^1 is as defined in formula (I) and L is a hydroxyl group may be formed by treatment of a compound of formula (IV) with a compound of formula R^1X where R^1 is as defined above and X is a leaving group such as bromide in the presence

of a base such as potassium *tert*-butoxide in an inert solvent such as DMSO at ambient temperature.



(IV)

Compounds of formula (IIB) where R^1, R^2 and R^3 are as defined in formula (I) may be prepared by treatment of a compound of formula (V):

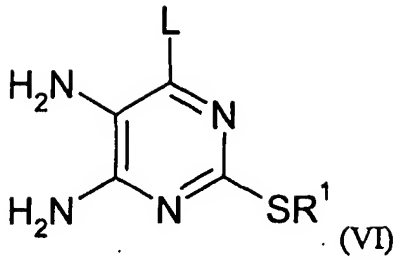


(V)

where R^1 is as defined in formula (I) and L is a leaving group such as bromo with an amine HNR^2R^3 where R^2 and R^3 are as defined in formula (I). The reaction may be carried out in a solvent such as *N*-methyl-pyrrolidine at a temperature between 0°C and 150°C.

Compounds of formula (V) where R^1 is as defined in formula (I) and L is a leaving group such as bromo may be prepared by treating a compound of formula (V) where R^1 is as defined above and L is NH_2 with a diazotizing agent such as isoamyl nitrite in the presence of a halogenating agent such as bromoform. The reaction may be performed in a solvent such as DMSO at a temperature between 0°C and 150°C.

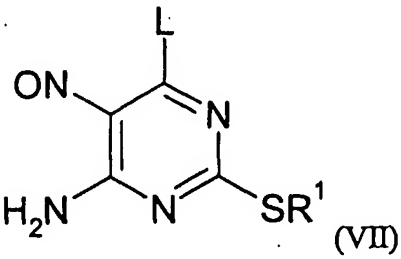
Compounds of formula (V) where R^1 is as defined in formula (I) and L is NH_2 may be prepared by treatment of a compound of formula (VI):



(VI)

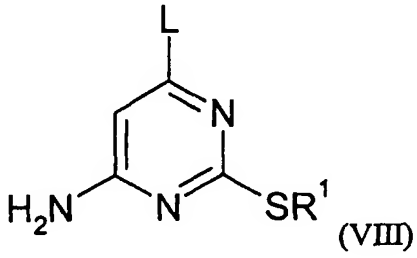
where R^1 and L are as defined above with ethyl glyoxylate in the presence of a base such as sodium methoxide in a solvent such as methanol at room temperature.

Compounds of formula (VI) where R^1 is as defined in formula (I) and L is NH_2 may be prepared by treating a compound of formula (VII) where R^1 and L are as defined above with a reducing agent such as sodium hydrosulphite. The reaction may be carried out in a solvent such as water at reflux.



(VII)

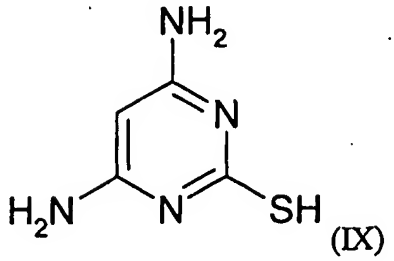
Compounds of formula (VII) where R^1 is as defined in formula (I) and L is NH_2 may be prepared by treating a compound of formula (VIII) where R^1 and L are as defined above with a nitrosating agent such as sodium nitrite. The reaction may be performed in a solvent such as aqueous acetic acid at a temperature between 0°C and 100°C.



(VIII)

Compounds of formula (VIII) where R^1 is as defined in formula (I) and L is NH_2 may be prepared by treating a compound of formula (IX) with a compound of formula R^1X where R^1 is as defined above and X is a leaving group such as bromide in the presence of a base

such as potassium *tert*-butoxide. The reaction may be performed in a solvent such as DMSO at room temperature.



(IX)

Compounds of formula (IV) or (IX) are either commercially available or are well known in the literature.

It will be appreciated by those skilled in the art that in the processes of the present invention certain functional groups such as hydroxyl or amino groups in the starting reagents or intermediate compounds may need to be protected by protecting groups. Thus, the preparation of the compounds of formula (I) may involve, at an appropriate stage, the removal of one or more protecting groups. The protection and deprotection of functional groups is fully described in 'Protective Groups in Organic Chemistry', edited by J. W. F. McOmie, Plenum Press (1973), and 'Protective Groups in Organic Synthesis', 2nd edition, T. W. Greene & P. G. M. Wuts, Wiley–Interscience (1991).

The compounds of formula (I) above may be converted to a pharmaceutically acceptable salt or solvate thereof, preferably a basic addition salt such as sodium, potassium, calcium, aluminium, lithium, magnesium, zinc, benzathine, chloroprocaine, choline, diethanolamine, ethanolamine, ethyldiamine, meglumine, tromethamine or procaine, or an acid addition salt such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, oxalate, methanesulphonate or *p*-toluenesulphonate.

The compounds of formula (I) have activity as pharmaceuticals, in particular as modulators of chemokine receptor (especially CXCR2) activity, and may be used in the treatment (therapeutic or prophylactic) of conditions/diseases in human and non-human animals which are exacerbated or caused by excessive or unregulated production of chemokines. Examples of such conditions/diseases include:

(1) **(the respiratory tract)** obstructive airways diseases including chronic obstructive pulmonary disease (COPD); asthma, such as bronchial, allergic,

intrinsic, extrinsic and dust asthma, particularly chronic or inveterate asthma (e.g. late asthma and airways hyper-responsiveness); bronchitis; acute, allergic, atrophic rhinitis and chronic rhinitis including rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca and rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous and pseudomembranous rhinitis and scrofoulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) and vasomotor rhinitis; sarcoidosis, farmer's lung and related diseases, fibroid lung and idiopathic interstitial pneumonia;

(2) **(bone and joints)** rheumatoid arthritis, seronegative spondyloarthropathies (including ankylosing spondylitis, psoriatic arthritis and Reiter's disease), Behcet's disease, Sjogren's syndrome and systemic sclerosis;

(3) **(skin)** psoriasis, atopical dermatitis, contact dermatitis and other eczmatous dermitides, seborrhoetic dermatitis, Lichen planus, Pemphigus, bullous Pemphigus, Epidermolysis bullosa, urticaria, angiodermas, vasculitides, erythemas, cutaneous eosinophilias, uveitis, Alopecia areata and vernal conjunctivitis;

(4) **(gastrointestinal tract)** Coeliac disease, proctitis, eosinopilic gastro-enteritis, mastocytosis, Crohn's disease, ulcerative colitis, food-related allergies which have effects remote from the gut, e.g., migraine, rhinitis and eczema;

(5) **(central and peripheral nervous system)** Neurodegenerative diseases and dementia disorders, e.g. Alzheimer's disease, amyotrophic lateral sclerosis and other motor neuron diseases, Creutzfeldt-Jacob's disease and other prion diseases, HIV encephalopathy (AIDS dementia complex), Huntington's disease, frontotemporal dementia, Lewy body dementia and vascular dementia; polyneuropathies, e.g. Guillain-Barré syndrome, chronic inflammatory demyelinating polyradiculoneuropathy, multifocal motor neuropathy, plexopathies; CNS demyelination, e.g. multiple sclerosis, acute disseminated/haemorrhagic encephalomyelitis, and subacute sclerosing panencephalitis; neuromuscular disorders, e.g. myasthenia gravis and Lambert-Eaton syndrome; spinal diorders, e.g. tropical spastic paraparesis, and stiff-man

syndrome: paraneoplastic syndromes, e.g. cerebellar degeneration and encephalomyelitis; CNS trauma; migraine; and stroke.

(6) **(other tissues and systemic disease)** atherosclerosis, Acquired Immunodeficiency Syndrome (AIDS), lupus erythematosus, systemic lupus, erythematosus, Hashimoto's thyroiditis, type I diabetes, nephrotic syndrome, eosinophilia fascitis, hyper IgE syndrome, lepromatous leprosy, and idiopathic thrombocytopenia pupura; post-operative adhesions, and sepsis.

(7) **(allograft rejection)** acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin and cornea; and chronic graft versus host disease;

(8) Cancers, especially non-small cell lung cancer (NSCLC), malignant melanoma, prostate cancer and squamous sarcoma, and tumour metastasis;

(9) Diseases in which angiogenesis is associated with raised CXCR2 chemokine levels (e.g. NSCLC, diabetic retinopathy).

(10) Cystic fibrosis, re-perfusion injury in the heart, brain, peripheral limbs and other organs.

(11) Burn wounds & chronic skin ulcers

(12) Reproductive Diseases (e.g. Disorders of ovulation, menstruation and implantation, Pre-term labour, Endometriosis)

Thus, the present invention provides a compound of formula (I), or a pharmaceutically-acceptable salt or solvate thereof, as hereinbefore defined for use in therapy.

Preferably the compounds of the invention are used to treat diseases in which the chemokine receptor belongs to the CXC chemokine receptor subfamily, more preferably the target chemokine receptor is the CXCR2 receptor,

Particular conditions which can be treated with the compounds of the invention are psoriasis, rheumatoid arthritis and diseases in which angiogenesis is associated with raised CXCR2 chemokine levels, and COPD. It is preferred that the compounds of the invention are used to treat rheumatoid arthritis.

As a further aspect of the present invention, certain compounds of formula (I) may have utility as antagonists of the CX3CR1 receptor. Such compounds are expected to be particularly useful in the treatment of disorders within the central and peripheral nervous system and other conditions characterized by an activation of microglia and/or infiltration of leukocytes (e.g. stroke/ischemia and head trauma).

In a further aspect, the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy.

In a still further aspect, the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for the treatment of human diseases or conditions in which modulation of chemokine receptor activity is beneficial.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

The invention still further provides a method of treating a chemokine mediated disease wherein the chemokine binds to a chemokine (especially CXCR2) receptor, which comprises administering to a patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined.

The invention also provides a method of treating an inflammatory disease, especially psoriasis, in a patient suffering from, or at risk of, said disease, which comprises administering to the patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined.

For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated.

The compounds of formula (I) and pharmaceutically acceptable salts and solvates thereof may be used on their own but will generally be administered in the form of a pharmaceutical composition in which the formula (I) compound/salt/solvate (active ingredient) is in association with a pharmaceutically acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.05 to 80 %w, still more preferably from 0.10 to 70 %w, and even more preferably from 0.10 to 50 %w, of active ingredient, all percentages by weight being based on total composition.

The present invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined, in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

The invention further provides a process for the preparation of a pharmaceutical composition of the invention which comprises mixing a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined, with a pharmaceutically acceptable adjuvant, diluent or carrier.

The pharmaceutical compositions may be administered topically (e.g. to the lung and/or airways or to the skin) in the form of solutions, suspensions, heptafluoroalkane aerosols and dry powder formulations; or systemically, e.g. by oral administration in the form of tablets, capsules, syrups, powders or granules; or by parenteral administration in the form of solutions or suspensions, or by subcutaneous administration or by rectal administration in the form of suppositories or transdermally. Preferably the compounds of the invention are administered orally.

The invention will now be further illustrated by reference to the following examples. In the examples the Nuclear Magnetic Resonance (NMR) spectra were measured on a Varian Unity Inova 300 or 400 MHz spectrometer and the Mass Spectrometry (MS) spectra measured on a Finnigan Mat SSQ7000 or Micromass Platform spectrometer. Where necessary, the reactions were performed under an inert atmosphere of either nitrogen or argon. Chromatography was generally performed using Matrex Silica 60® (35-70 micron)

or Prolabo Silica gel 60® (35-70 micron) suitable for flash silica gel chromatography. High pressure liquid chromatography purification was performed using either a Waters Micromass LCZ with a Waters 600 pump controller, Waters 2487 detector and Gilson FC024 fraction collector or a Waters Delta Prep 4000. The abbreviations m.p. and DMSO used in the examples stand for melting point and dimethyl sulphoxide respectively.

EXAMPLES

Example 1

5-[[(2,3-difluorophenyl)methyl]thio]-7-[[(1*R*)-2-hydroxy-1-methylethyl]amino]-thiazolo[4,5-*d*]pyrimidine-2(3*H*)-thione

a) 2-Amino-5-[[(2,3-difluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7(4*H*)-one

Potassium *t*-butoxide solution (0.45ml of 1M solution in tetrahydrofuran) was added to a stirred solution of 2-amino-5,6-dihydro-5-thioxo-thiazolo[4,5-*d*]pyrimidin-7(*4H*)-one (0.09g) [Cited: Indian J. Chem., Sect. B (1989), 28B(11), 964-5.] and 2,3-difluorobenzyl bromide in dimethyl sulphoxide (2ml). After stirring for 3 days, the reaction mixture was poured onto water to give the subtitled compound, isolated by filtration.

MS (APCI) 327 ($M+H^+$, 100%).

(b) 7-Chloro-5-[[(2,3-difluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-2-amine

The product from example 1, step (a) (0.89g), phosphorus oxychloride (12ml) and *N,N*-dimethylaniline (1.2ml) were heated at reflux for 2 hours. The cooled reaction mixture was poured onto ice water and stirred for 2 hours. Chromatography (SiO_2, methanol/dichloromethane as eluant) gave the subtitled compound.

m.p. 217-218.5°C
MS (APCI) 346(M+H, 100%).

(c) (2*R*)-2-[[2-amino-5-[[(2,3-difluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-1-propanol,

The product from example 1, step (b) (70.0g) and (*R*)-1-amino-propan-2-ol (32 ml) in N-methylpyrrolidinone (600ml) and Hunigs base (71 ml) was heated at 110°C for 16 hours. The mixture was poured into water (5L) and the crude product collected at by filtration. This solid was purified by recrystallisation from acetonitrile (2.5 L) to give 65g of the subtitled compound.

MS (APCI) 384 (M+H, 100%).

(d) (2R)-2-[[2-chloro-5-[[(2,3-difluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-1-propanol,

The product from example 1, step (c) (0.5g) was dissolved in concentrated hydrochloric acid (18 ml). To this solution was added a mixture of acetonitile (8 ml) and water (16 ml), maintaining the temperature below 20°C. The solution was then coled in an ice bath and a solution of sodium nitrite (0.135g) in water (0.5 ml) added. Upon completion of addition the mixture was allowed to stir for a further 1 hour. The solid was then collected by filtration, washed well with water and dried at 40°C *in vacuo* to give the subtitled compound (0.43g).

MS (APCI) 403 (M+H, 100%).

(e) 5-[[(2,3-difluorophenyl)methyl]thio]-7-[[(1*R*)-2-hydroxy-1-methylethyl]amino]-thiazolo[4,5-*d*]pyrimidine-2(3*H*)-thione,

A mixture of the product from example 1, step (d) (150 mg) and sodium hydrosulfide (150 mg) in DMSO (5 ml) was stirred at room temperature for 30 mins. The mixture was poured into water (100 ml) and the pH adjusted to 7 and the product collected by filtration and purified by chromatography (SiO_2, ethyl acetate/dichloromethane as eluant) to give the title compound (67 mg).

MS (APCI) 401 (M+H, 100%).
NMR δH (d_6-DMSO) 14.06 (1H, s), 7.75 (1H, d), 7.45-7.11 (3H, m), 4.75 (1H, bs), 4.41 (2H, m), 4.21 (1H, bs), 3.46-3.32 (2H, m), 1.09 (3H, d).

Example 2

2-[[(2,3-Difluorophenyl)methyl]thio]-4-[[(1*R*)-2-hydroxy-1-methylethyl]amino]-7(8*H*)-pteridinone

a) 2-[[(2,3-Difluorophenyl)methyl]thio]- 4,6-pyrimidinediamine

4,6-diamino-2-pyrimidinethiol (7.3g) was dissolved in DMSO (100ml) at room temperature under an atmosphere of nitrogen. Potassium *tert*-butoxide (1M in THF, 48.3ml) was added followed by 2,3-difluorobenzyl-bromide (10.0g). The mixture was stirred for 2 hours at room temperature. The reaction mixture was then partitioned between ethyl acetate and ammonium chloride. The organic phase was washed with ammonium chloride (3x) and brine, then dried over magnesium sulphate and evaporated to give the subtitled product as a white solid (12.2g)

MS: ADCI (+ve) 269 (M+1)

b) 2-[[(2,3-Difluorophenyl)methyl]thio]-5-nitroso-4,6-pyrimidinediamine

The product of example 2, step (a) (2.5g) was dissolved in acetic acid (150ml) and the solution cooled to 5°C. A solution of sodium nitrite (625mg) in water (50ml) was added dropwise resulting in a dark blue colouration. The reaction was stirred at room temperature for 30 minutes during which time a pink solid precipitated from solution. This was isolated by filtration and washed with water, then dried at 50°C to give the sub-titled product as a blue solid (4.14g)

MS: ADCI (+ve) 298 (M+1)
^{1}H NMR: δ (DMSO) 4.44 (s,2H), 7.13-7.54 (m,3H), 8.13 (s,1H), 8.51 (s,1H), 9.10 (s,1H), 10.18 (s,1H).

c) 2-[[(2,3-Difluorophenyl)methyl]thio]- 4,5,6-pyrimidinetriamine

To a suspension of the product of example 2, step (b) (2g) in boiling water (40ml) was added $Na_2S_2O_4$ (5.4g) portion-wise. The suspension was allowed to cool and then 50% sulphuric acid was added slowly and then the mixture was cooled to 0°C. The solid was isolated by filtration and washed with cold water, then dried over P_2O_5 at 50°C to give the sub-titled product as a yellow solid.

MS: ADCI (+ve) 284 (M+1)
^{1}H NMR: δ (DMSO) 4.33 (s,2H), 6.42 (brs,3H), 7.10-7.48 (m,3H)

d) 4-amino-2-[[(2,3-difluorophenyl)methyl]thio]- 7(8*H*)-pteridinone

The product of example 2, step (c) (100mg) was dissolved in a solution of sodium (0.05g) in methanol (5ml). This was left to stir for 15 min at room temperature, then ethyl glyoxalate (134µl) was added to the mixture which was left to stir for 12hr at room temperature. Water (5ml) was added, then concentrated hydrochloric acid was slowly added to acidify the solution to ~ pH5 whereupon a solid precipitated which was isolated by filtration and dried over P_2O_5 at 50°C to yield a pale yellow solid (44.5mg).

MS: ADCI (+ve) 322 (M+1)
^{1}H NMR: δ (DMSO) 4.18 (s,2H), 7.11-7.58 (m,3H), 7.84 (s,1H), 12.69 (bs,1H)

e) 4-bromo-2-[[(2,3-difluorophenyl)methyl]thio]-7(8*H*)-pteridinone

The product of example 2, step (d) (6.0g) was suspended in DMSO (90ml) and bromoform (60ml) was added and the mixture was heated to 100°C. Isopentylnitrite (25ml) was added and the mixture stirred for 5min. The mixture was quickly cooled in an ice bath then evaporated to leave an oil. This was repeated three times. Acetonitrile (200ml) was added and the solid which separated was removed by filtration. The solvent was evaporated and the residue was purified by flash chromatography, eluting with dichloromethane and then 5% ethyl acetate in dichloromethane to give a yellow solid which was slurried with ether then collected. The solid was washed with ether and dried to give the subtitled compound as a colourless solid (8.74g).

MS: APCI (-ve) 382/4 (M-H), 382 (100%)
^{1}H NMR: δ (DMSO) 4.47 (s, 2H), 7.13-7.55 (m,3H), 8.14 (s,1H), 13.33 (bs,1H)

f) 2-[[(2,3-difluorophenyl)methyl]thio]-4-[[(1*R*)-2-hydroxy-1-methylethyl]amino]-7(8*H*)-pteridinone

The product of example 2, step (e) (8.7g) was dissolved in *N*-methylpyrrolidinone (40ml) and Hunigs base (7.9ml) was added followed by D-alaninol (2.7ml). The mixture was stirred at 100°C for 15mins. The cooled solution was poured onto water, (1l), and acidified with dilute hydrochloric acid. The solid which separated was collected, washed with water and air dried. Crystallisation from acetonitrile afforded the title compound as a pale yellow solid (7.4g).

m.p. 215-217°C

MS: APCI (+ve) 380 (M+H, 100%)

^{1}H NMR: δ (DMSO) 1.14 (d, 3H), 3.48 (m, 2H), 4.31 (m, 1H), 4.45 (dd, 2H) 4.82 (t, 1H) 7.15 (m, 1H), 7.33 (m, 1H), 7.47 (t, 1H), 7.76 (d, 1H), 7.83 (d,1H), 12.70 (s, 1H).

g) 2-[[(2,3-Difluorophenyl)methyl]thio-4-[[(1R)-2-hydroxy-1-methylethyl]amino-7(8H)-pteridinethione

The product of example 2, step (f) (0.50g) and Lawessons reagent (1.06g) were stirred in dioxan (10mL) and heated under reflux for 30 mins. Water (5mL) was added and heating continued for 10 mins. The cooled mixture was diluted with water to give a suspension. The solid was collected, washed with water and dried. Purification by fl;ash chromatography over silica using dichloromethane/acetonitrile (5-10%) as eluant afforded the title compound 0.225g.

mp 232-233°C

MS: APCI 396 (M+H, 100%)

^{1}H NMR: δ (DMSO) 1.15(d, 3H), 3.47 (m, 2H), 4.30 (m, 1H), 4.46 (q, 2H), 4.82 (bm, 1H), 7.16 (m, 1H), 7.34 (m, 1H), 7.53 (t, 1H), 8.10 (d, 1H), 8.21 (s,1H), 14.45 (s, 1H).

Pharmacological Data

Ligand Binding Assay

[^{125}I]IL-8 (human, recombinant) was purchased from Amersham, U.K. with a specific activity of 2,000Ci/mmol. All other chemicals were of analytical grade. High levels of hrCXCR2 were expressed in HEK 293 cells (human embryo kidney 293 cells ECACC No. 85120602) (Lee *et al.* (1992) *J. Biol. Chem.* **267** pp16283-16291). hrCXCR2 cDNA was amplified and cloned from human neutrophil mRNA. The DNA was cloned into PCRScript (Stratagene) and clones were identified using DNA. The coding sequence was sub-cloned into the eukaryotic expression vector RcCMV (Invitrogen). Plasmid DNA was prepared using Quiagen Megaprep 2500 and transfected into HEK 293 cells using Lipofectamine reagent (Gibco BRL). Cells of the highest expressing clone were harvested in phosphate-buffered saline containing 0.2%(w/v) ethylenediaminetetraacetic acid (EDTA) and centrifuged (200g, 5min.). The cell pellet was resuspended in ice cold homogenisation buffer [10mM HEPES (pH 7.4), 1mM dithiothreitol, 1mM EDTA and a panel of protease inhibitors (1mM phenyl methyl sulphonyl fluoride, 2μg/ml soybean trypsin inhibitor, 3mM benzamidine, 0.5μg/ml leupeptin and 100μg/ml bacitracin)] and the cells left to swell for 10 minutes. The cell preparation was disrupted using a hand held glass mortar/PTFE pestle homogeniser and cell membranes harvested by centrifugation (45 minutes, 100,000g, 4°C). The membrane preparation was stored at -70°C in homogenisation buffer supplemented with Tyrode's salt solution (137mM NaCl, 2.7mM KCl, 0.4mM NaH_2PO_4), 0.1%(w/v) gelatin and 10%(v/v) glycerol.

All assays were performed in a 96-well MultiScreen 0.45μm filtration plates (Millipore, U.K.). Each assay contained ~50pM [^{125}I]IL-8 and membranes (equivalent to ~200,000 cells) in assay buffer [Tyrode's salt solution supplemented with 10mM HEPES (pH 7.4), 1.8mM $CaCl_2$, 1mM $MgCl_2$, 0.125mg/ml bacitracin and 0.1%(w/v) gelatin]. In addition, a compound of formula (I) according to the Examples was pre-dissolved in DMSO and added to reach a final concentration of 1%(v/v) DMSO. The assay was initiated with the addition of membranes and after 1.5 hours at room temperature the membranes were harvested by filtration using a Millipore MultiScreen vacuum manifold and washed twice with assay buffer (without bacitracin). The backing plate was removed from the MultiScreen plate assembly, the filters dried at room temperature, punched out and then counted on a Cobra γ-counter.

The compounds of formula (I) according to the Examples were found to have IC_{50} values of less than (<) 10μM.

Intracellular Calcium Mobilisation Assay

Human neutrophils were prepared from EDTA-treated peripheral blood, as previously described (Baly *et al.* (1997) Methods in Enzymology 287 pp70-72), in storage buffer [Tyrode's salt solution (137mM NaCl, 2.7mM KCl, 0.4mM NaH_2PO_4) supplemented with 5.7mM glucose and 10mM HEPES (pH 7.4)].

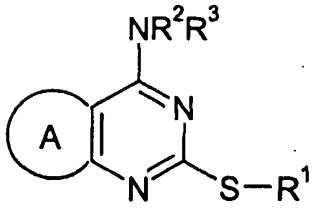
The chemokine GROα (human, recombinant) was purchased from R&D Systems (Abingdon, U.K.). All other chemicals were of analytical grade. Changes in intracellular free calcium were measured fluorometrically by loading neutrophils with the calcium sensitive fluorescent dye, fluo-3, as described previously (Merritt *et al.* (1990) Biochem. J. 269, pp513-519). Cells were loaded for 1 hour at 37°C in loading buffer (storage buffer with 0.1%(w/v) gelatin) containing 5μM fluo-3 AM ester, washed with loading buffer and then resuspended in Tyrode's salt solution supplemented with 5.7mM glucose, 0.1%(w/v) bovine serum albumin (BSA), 1.8mM $CaCl_2$ and 1mM $MgCl_2$. The cells were pipetted into black walled, clear bottom, 96 well micro.plates (Costar, Boston, U.S.A.) and centrifuged (200g, 5 minutes, room temperature).

A compound of formula (I) according to the Examples was pre-dissolved in DMSO and added to a final concentration of 0.1%(v/v) DMSO. Assays were initiated by the addition of an A_{50} concentration of GROα and the transient increase in fluo-3 fluorescence (λ_{Ex} =490nm and λ_{Em} = 520nm) monitored using a FLIPR (Fluorometric Imaging Plate Reader, Molecular Devices, Sunnyvale, U.S.A.).

The compounds of formula (I) according to the Examples were tested and found to be antagonists of the CXCR2 receptor in human neutrophils.

CLAIMS

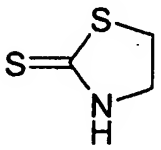
1. A compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof:



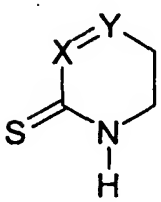
(I)

in which:

A is a group of formula (a) or (b):



(a)



(b)

R^1 represents a C_3-C_7 carbocyclic, C_1-C_8 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl group, each of which may be optionally substituted by one or more substituent groups independently selected from halogen atoms, $-OR^4$, $-NR^5R^6$, $-CONR^5R^6$, $-COOR^7$, $-NR^8COR^9$, $-SR^{10}$, $-SO_2R^{10}$, $-SO_2NR^5R^6$, $-NR^8SO_2R^9$, an aryl or heteroaryl group, which last two may themselves be optionally substituted by one or more substituents independently selected from halogen atoms, cyano, nitro, $-OR^4$, $-NR^5R^6$, $-CONR^5R^6$, $-COOR^7$, $-NR^8COR^9$, $-SR^{10}$, $-SO_2R^{10}$, $-SO_2NR^5R^6$, $-NR^8SO_2R^9$, C_1-C_6 alkyl or trifluoromethyl groups;

R^2 and R^3 each independently represent a hydrogen atom, or a C_3-C_7 carbocyclic,

C_1-C_8 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl group, the latter four groups may be optionally substituted by one or more substituent groups independently selected from:

(a) halogen atoms, $-OR^4$, $-NR^5R^6$ $-CONR^5R^6$, $-COOR^7$, $-NR^8COR^9$, $-SR^{10}$, $-SO_2R^{10}$, $-SO_2NR^5R^6$, $-NR^8SO_2R^9$;

(b) a 3-8 membered ring optionally containing one or more atoms selected from O, S, NR^8 and itself optionally substituted by C_1-C_3-alkyl or halogen; or

(c) an aryl group or heteroaryl group each of which may be optionally substituted by one or more substituents independently selected from halogen atoms, cyano, nitro, $-OR^4$, $-NR^5R^6$, $-CONR^5R^6$, $-NR^8COR^9$, $-SO_2NR^5R^6$, $-NR^8SO_2R^9$, C_1-C_6 alkyl and trifluoromethyl groups;

R^4 represents hydrogen, C_1-C_6 alkyl or a phenyl group the latter two of which may be optionally substituted by one or more substituent groups independently selected from halogen atoms, phenyl, $-OR^{11}$ and $-NR^{12}R^{13}$

R^5 and R^6 independently represent a hydrogen atom or a C_1-C_6 alkyl or phenyl group the latter two of which may be optionally substituted by one or more substituent groups independently selected from halogen atoms, phenyl, $-OR^{14}$ and $-NR^{15}R^{16}$, $-CONR^{15}R^{16}$, $-NR^{15}COR^{16}$, $-SONR^{15}R^{16}$, $NR^{15}SO_2R^{16}$

or

R^5 and R^6 together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocyclic ring system optionally containing a further heteroatom selected from oxygen and nitrogen atoms, which ring system may be optionally substituted by one or more substituent groups independently selected from phenyl, $-OR^{14}$, $-COOR^{14}$, $-NR^{15}R^{16}$, $-CONR^{15}R^{16}$, $-NR^{15}COR^{16}$, $-SONR^{15}R^{16}$, $NR^{15}SO_2R^{16}$ or C_1-C_6 alkyl, itself optionally substituted by one or more substituents independently selected from halogen atoms and $-NR^{15}R^{16}$ and $-OR^{17}$ groups;

R^{10} represents a C_1-C_6-alkyl or a phenyl group, either of which may be optionally substituted by one or more substituent groups independently selected from halogen atoms, phenyl, $-OR^{17}$ and $-NR^{15}R^{16}$,

X is CH or CCN,

Y is N or CR^{18}, and

each of R^7, R^8, R^9, R^{11}, R^{12}, R^{13}, R^{14} R^{15}, R^{16}, R^{17} and R^{18} independently represents a hydrogen atom or a C_1-C_6, alkyl, or a phenyl group.

2. A compound according to claim 1, wherein R^1 represents an optionally substituted benzyl group.

3. A compound according to claim 1 or claim 2, wherein one of R^2 and R^3 is hydrogen and the other is C_1-C_8 alkyl substituted by hydroxy and one or more methyl or ethyl groups.

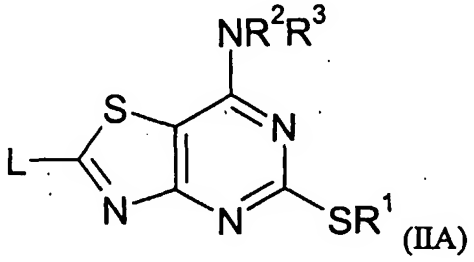
4. A compound according to any one of claims 1 to 3 in which A is a group of formula (a).

5. A compond according to any one of claims 1 to 3 in which A is a group of formula (b).

6. A compound according to claim 5 in which X is CH and Y is N.

7. A compound according to claim 1 selected from:
-[[(2,3-difluorophenyl)methyl]thio]-7-[[(1*R*)-2-hydroxy-1-methylethyl]amino]-thiazolo[4,5-*d*]pyrimidine-2(3*H*)-thione,
2-[[(2,3-difluorophenyl)methyl]thio]-4-[[(1*R*)-2-hydroxy-1-methylethyl]amino]-7(8*H*)-pteridinethione,
and pharmaceutically acceptable salts thereof.

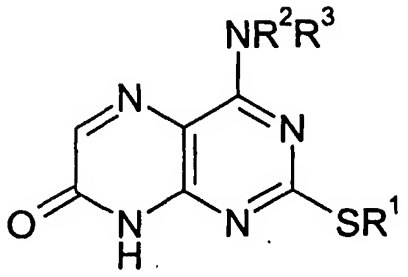
8. A process for the preparation of a compound of formula (I) which comprises:
(a) treatment of a compound of formula (IIA):



(IIA)

where R^1, R^2 and R^3 are as defined in formula (I) or are protected derivatives thereof and L is a leaving group with a metal hydrosulphide, or

(b) treatment of a compound of formula (IIB):



(IIB)

where R^1, R^2 and R^3 are as defined in formula (I) or are protected derivatives thereof with a thiating agent, and optionally thereafter process (a) or (b) and in any order:

- removing any protecting groups
- forming a pharmaceutically acceptable salt.

9. A pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 7 in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

10. A process for the preparation of a pharmaceutical composition as claimed in claim 9 which comprises mixing a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 7 with a pharmaceutically acceptable adjuvant, diluent or carrier.

11. A compound of formula (I), or a pharmaceutically-acceptable salt or solvate thereof, as claimed in any one of claims 1 to 7 for use in therapy.

12. Use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 7 in the manufacture of a medicament for use in therapy.

13. A method of treating a chemokine mediated disease wherein the chemokine binds to one or more chemokine receptors, which comprises administering to a patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 7.

14. A method according to claim 13 in which the chemokine receptor belongs to the CXC chemokine receptor subfamily.

15. A method according to claim 13 or 14 in which the chemokine receptor is the CXCR2 receptor.

16. A method of treating an inflammatory disease in a patient suffering from, or at risk of, said disease, which comprises administering to the patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 7.

17. A method according to claim 16, wherein the disease is psoriasis, rheumatoid arthritis or COPD.

18. A method according to claim 16, wherein the disease is rheumatoid arthritis.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 02/00731

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 513/04, C07D 475/06, C07D 471/04, A61K 31/519, A61P 11/00, A61P 17/06, A61P 29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-INTERNAL, WPI DATA, PAJ, CHEM.ABS.DATA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 0125242 A1 (ASTRAZENECA UK LIMITED), 12 April 2001 (12.04.01) --	1-18
P,X	WO 0158906 A1 (ASTRAZENECA AB), 16 August 2001 (16.08.01) --	1-18
P,X	WO 0158907 A1 (ASTRAZENECA AB), 16 August 2001 (16.08.01) --	1-18
P,X	WO 0162758 A1 (ASTRAZENECA AB), 30 August 2001 (30.08.01) --	1-18

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 June 2002	13 -06- 2002
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer GERD STRANDELL/BS Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 02/00731

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 0009511 A1 (ASTRA PHARMACEUTICALS LTD.), 24 February 2000 (24.02.00), page 56 - page 57, the claims --	1-18
X	WO 0119825 A1 (WARNER-LAMBERT COMPANY), 22 March 2001 (22.03.01), claims 1,12,14 --	1-18
A	WO 0039129 A1 (K.U. LEUVEN RESEARCH & DEVELOPMENT), 6 July 2000 (06.07.00), page 19, line 8 - line 13, claim 1 -- --------	1-18

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE02/00731

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 13-18
because they relate to subject matter not required to be searched by this Authority, namely:

see next sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Claims 13-18 relate to methods of treatment of the human or animal body by surgery or by therapy/ diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

INTERNATIONAL SEARCH REPORT

Information on patent family members

01/05/02

International application No.
PCT/SE 02/00731

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0125242 A1	12/04/01	AU 7304900 A	10/05/01
		SE 9903544 D	00/00/00
WO 0158906 A1	16/08/01	AU 3255601 A	20/08/01
		AU 6456300 A	13/03/01
		GB 0003022 D	00/00/00
		GB 2359079 A	15/08/01
		NO 20020712 D	00/00/00
		AU 6306100 A	19/02/01
		GB 0003023 D	00/00/00
		GB 2359080 A	15/08/01
WO 0158907 A1	16/08/01	AU 3427301 A	20/08/01
		AU 6456500 A	13/03/01
		GB 0003025 D	00/00/00
		GB 2359081 A	15/08/01
		NO 20020604 A	07/02/02
WO 0162758 A1	30/08/01	AU 1042101 A	08/05/01
		AU 3431601 A	03/09/01
		GB 0004128 D	00/00/00
		GB 2359551 A	29/08/01
WO 0009511 A1	24/02/00	AU 5662599 A	06/03/00
		EP 1104425 A	06/06/01
		SE 9802729 D	00/00/00
WO 0119825 A1	22/03/01	AU 5629500 A	17/04/01
WO 0039129 A1	06/07/00	AU 3042900 A	31/07/00
		BR 9911979 A	27/03/01
		EP 1097089 A	09/05/01
		EP 1144412 A	17/10/01
		US 6015061 A	18/01/00
		WO 0002791 A	20/01/00